



(19) Europäisches Patentamt

European Patent Office

Office européen des brevets



(11) EP 0 890 359 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
02.05.2002 Bulletin 2002/18

(51) Int Cl.7: **A61K 31/545, A61K 9/20,
A61K 47/30, A61K 47/38**

(21) Application number: **97904616.6**

(86) International application number:
PCT/JP97/00509

(22) Date of filing: **21.02.1997**

(87) International publication number:
WO 97/31639 (04.09.1997 Gazette 1997/38)

(54) TABLETS CONTAINING BETA-LACTAM ANTIBIOTIC AND PROCESS FOR PRODUCING THE SAME

BETA-LACTAM-ANTIBIOTIKUM ENTHALTENDE TABLETTEN UND VERFAHREN ZU DEREN HERSTELLUNG

COMPRIMES CONTENANT UN ANTIBIOTIQUE AU BETA-LACTAME ET PROCEDE POUR LEUR PRODUCTION

(84) Designated Contracting States:
**AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL
PT SE**

(56) References cited:
**WO-A-92/08463 WO-A-92/19227
DE-A- 2 251 250 FR-A- 2 722 984
JP-A- 6 183 964 JP-A- 7 324 101
JP-A- 50 140 623 JP-A- 58 109 419
JP-A- 60 011 414 JP-A- 63 301 820**

(30) Priority: **29.02.1996 JP 4274396
29.11.1996 JP 32026496**

(43) Date of publication of application:
13.01.1999 Bulletin 1999/02

- **CHEMICAL ABSTRACTS, vol. 112, no. 13, 26 March 1990 Columbus, Ohio, US; abstract no. 117620, XP002077993 & JP 01 206969 A (TAKEDA CHEMICAL INDUSTRIES LTD.,JP) 21 August 1989**
- **CHEMICAL ABSTRACTS, vol. 112, no. 4, 22 January 1990 Columbus, Ohio, US; abstract no. 25681, XP002077994 & JP 01 149728 A (FUJISAWA PHARMACEUTICAL CO. LTD.,JP) 12 June 1989**
- **"General Techniques for New Pharmaceutical Preparation Development Systems - Bases and Filling Material (in Japanese)", Edited by SADAO IGUCHI, R & D PLANNING, 12 July 1985, pages 417-418, 432-436.**
- **"Drug Handbook (in Japanese)", 5th Edition, Edited by OSAKA-FU HOSPITAL PHARMACISTS ASSOC., YAKUGYO JIHOSHA, 5 February 1995, pages 1940-1941, 2358-2359.**

(60) Divisional application:
01123407.7 / 1 166 651

(73) Proprietor: **FUJISAWA PHARMACEUTICAL CO., LTD.
Osaka-shi Osaka 541-8514 (JP)**

(72) Inventor: **YAMAGUCHI, Hisami
Toyono-gun, Osaka 563-01 (JP)**

(74) Representative:
**Gille Hrabal Struck Neidlein Prop Roos
Patentanwälte
Brücknerstrasse 20
40593 Düsseldorf (DE)**

EP 0 890 359 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description**TECHNICAL FIELD**

5 [0001] This invention relates to β -lactam antibiotic-containing tablets and a method of producing the same. More particularly, it relates to tablets of the above variety which can be orally taken either as such or, for taking by, for example, the aged who have difficulties in swallowing, as a dispersion available upon dropping the same into water in a glass for self-disintegration, and to a method of producing the same.

10 BACKGROUND TECHNOLOGY

[0002] Particularly in Europe and America, where β -lactam antibiotics such as cefixime and cefdinir are administered generally in single doses of as great as 200 mg to 400 mg potency, unit dosage forms, whether they are capsules or tablets, have to be considerably large in size. When 400 mg potency capsules are prepared, for instance, the capsule 15 size reaches approximately No. 0, so that not only patients having difficulties in swallowing but also ordinary adult patients become reluctant to take them or get a repulsive sensation in taking them. Such capsules are indeed difficult to take. In the case of tablets, too, 400 mg potency tablets generally weigh 700 to 1,000 mg per tablet and accordingly are large-sized.

[0003] The problems encountered in taking such large dosage forms give an unnecessary sensation of oppression 20 to patients on the occasion of taking them. Improvements in their administrability have thus been required.

[0004] Therefore, the present inventor attempted to provide a dosage form with improved administrability by reducing the tablet size as much as possible to thereby facilitate the taking of tablets by the recipient and at the same time to provide a dosage form capable of being taken in the form of a dispersion resulting from rapid self-disintegration upon its being simply dropped into water or the like in a glass, for instance, to thereby make said dosage form administrable 25 to persons of advanced age or children having difficulties in swallowing the dosage form as such. The expression "rapid self-disintegration" as used herein means that when the preparation is dropped into a glass containing a liquid such as water, the tablet form spontaneously collapses generally within 3 minutes, preferably within 1 minute, so that said preparation can be orally taken in dispersion form without awaiting long before taking.

[0005] It is indeed easy to produce tablets capable of self-disintegrating very rapidly by incorporating an effervescent 30 agent comprising a combination of sodium hydrogen carbonate and tartaric acid, for instance. However, when such tablets are orally taken, they give off bubbles in the oral cavity, so that patients feel a discomfort or an unnecessary sensation of anxiety. For securing a good shelf-life in a humid environment, it is necessary to use a moisture-proof packaging material, which increases the production cost. Therefore, in developing the dosage form which the present invention is intended to provide, it has been a tough problem to find out a formulation enabling very rapid self-disinte- 35 gration without the aid of any effervescent component.

[0006] For producing β -lactam antibiotic-containing tablets which can be easily ingested as they are and be also ingested in the form of a dispersion resulting from self-disintegration thereof, a technology is described in European Patent EP 0281200 B (corresponding Japanese patent application: Kokai Tokkyo Koho S63-301820), which comprises adding 24 to 70% by weight, based on the weight of the β -lactam antibiotic, of microcrystalline cellulose or microfine 40 cellulose as a first disintegrator and 2 to 20% by weight, on the same basis, of low-substituted hydroxypropylcellulose or the like as a second disintegrator.

[0007] However, said first disintegrator, which is used in a large amount, increases the tablet size. In addition, the proportion of a binder component for wet granulation is as low as 0 to 0.1% by weight based on the antibiotic, hence is substantially nil. This is because the use of a binder renders tablets extremely poor in self-disintegrating properties.

45 In the process for producing these tablets, in which no binder is used, a special method of insuring an integrity of the artefact is employed which comprises mixing the antibiotic bulk substance with microcrystalline cellulose and kneading the mixture with the aid of water under application of a great deal of force, without using any alcohol. As a result, large lumps are formed inevitably and they are milled in the wet state and then dried, followed by further milling to provide granules for tableting. It is a problem that these steps are very inefficient.

50 [0008] Meanwhile, tablets containing amoxicillin, which is a β -lactam antibiotic, are commercially available under the trade name of Flemoxin Solutab 500® from Brocades Pharma (Netherlands), the patentee to whom said European patent has been granted. Said tablets each contains 500 mg potency (about 570 mg) of amoxicillin and weighs about 970 mg, hence is very large and not entirely suited for oral administration.

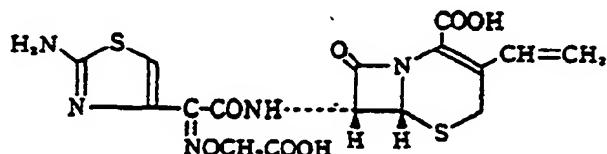
[0009] Most β -lactam antibiotics are bitter. Therefore, aqueous dispersions prepared from tablets containing them, 55 when orally taken, give a bitter taste, although the tablets, when taken as such, taste not so bitter. For masking the bitter taste, it thus becomes necessary to incorporate a sweetener, preferably a synthetic sweetener which is effective at low addition levels and thus suited for tablet miniaturization. However, when a commercial synthetic sweetener is incorporated, a problem arises, namely the self-disintegrating properties of tablets become poor, since synthetic sweet-

eners are soluble in water and become viscous and sticky.

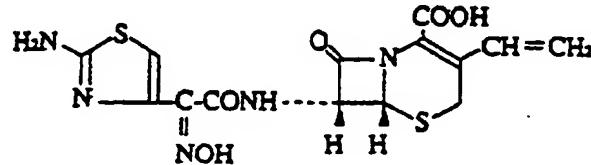
DISCLOSURE OF THE INVENTION

- 5 [0010] In an attempt to develop a method of improving the rate of self-disintegration of tablets and at the same time miniaturizing the same, the present inventor made investigations concerning the disintegrator species to be used, the level of addition thereof, the binder addition level, the synthetic sweetener particle size and the method of incorporating the same, among others and, as a result, the inventor invented β -lactam antibiotic-containing tablets which are small-sized, show good self-disintegrating properties and can be produced by a conventional method.
- 10 [0011] Furthermore, the inventor found that when granulation is performed using ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol, tablets showing better dispersibility upon self-disintegration can be obtained.
- [0012] The β -lactam antibiotic-containing tablets of this invention contain, per tablet, 60 to 85% by weight of an β -lactam antibiotic, 1 to 10% by weight of low-substituted hydroxypropylcellulose and/or crosslinked polyvinylpyrrolidone
- 15 as a disintegrator, and 0.5 to 2% by weight of a binder.
- [0013] Preferably, the β -lactam antibiotic-containing tablets of this invention further contain, per tablet, 0.5 to 15% by weight of a synthetic sweetener and/or a granulated synthetic sweetener.
- [0014] The β -lactam antibiotic-containing tablet production method of this invention is characterized in that the above specified respective proportions of a β -lactam antibiotic, the disintegrator and a binder, optionally together with one or
- 20 more excipients, are granulated, optionally mixing the granulated product with a synthetic sweetener and/or a granulated synthetic sweetener and further additives and compressing the mixture.
- [0015] Granulating the mixture with ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol leads to β -lactam antibiotic-containing tablets with further improved properties.
- [0016] The β -lactam antibiotic to be used in the practice of this invention is one capable of producing a beneficial effect upon oral administration and includes, for example, cefixime and cefdinir respectively represented by the structural formulas shown below as well as cefaclor, cefroxadine, cefadroxil, cefaloglycin, cefalexin, cefradine, amoxicillin, ampicillin and the like.

Cefixime



Cefdinir



- 50 [0017] Each tablet contains such β -lactam antibiotic in a proportion of 60 to 85% by weight, preferably 65 to 80% by weight.
- [0018] As a result of investigations concerning the disintegrator species to be used in the practice of this invention and the level of addition thereof, it was found that, as compared with such salt type disintegrators as ECG 505 (trademark; carboxymethylcellulose calcium), Ac-Di-Sol (trademark; crosslinked carboxymethylcellulose sodium) and Pri-mojel (trademark; starch glycolic acid sodium), nonion type disintegrators, such as low-substituted hydroxypropylcellulose (L-HPC) and crosslinked polyvinylpyrrolidone, can produce a very good disintegrating effect even when they are added in small proportions. Low-substituted hydroxypropylcellulose is a product derived from cellulose by partial substitution with the 2-hydroxypropoxy group, the degree of substitution being not higher than 25%, preferably 7 to 16%.
- 55 [0019] Generally, low-substituted hydroxypropylcellulose and crosslinked polyvinylpyrrolidone are incorporated in

tablets independently, although both may be used combinedly.

[0020] Such disintegrator is used in a proportion of 1 to 10% by weight, preferably 3 to 8% by weight, on a per-tablet basis.

[0021] The tablets of this invention further contain binder as an essential constituent. The addition of a binder has an adverse effect on the self-disintegrating properties of tablets, hence is not desirable from the self-disintegration viewpoint. However, the production of tablets without adding any binder give such inconveniences as mentioned herein before.

[0022] The inventor of this invention made investigations in search of binder species which would not give adverse effects on the self-disintegrating properties of tablets as well as investigations concerning the addition level thereof.

10 The binders according to the invention are polyvinylpyrrolidone; hydroxypropylcellulose, preferably low-viscosity type hydroxypropylcellulose, and hydroxypropylmethylcellulose, whereby polyvinylpyrrolidone is most preferred.

[0023] When these binders are used in an amount of 0.5 to 2% by weight, preferably 0.8 to 1.5% by weight, on a per-tablet basis, tablets which can self-disintegrate rapidly can be produced by a conventional production method.

15 [0024] Since β -lactam antibiotics, for example cefixime and cefdinir, have a strongly bitter taste, it is necessary to add a synthetic sweetener in cases where tablets are to be taken in the form of dispersions after self-disintegration in water, for instance, though this is not always necessary in cases where tablets are to be taken as such.

[0025] As regards the synthetic sweetener addition level, which may vary according to the synthetic sweetener species and the active ingredient β -lactam antibiotic, the sweetener is incorporated in tablets generally in a proportion of 0.5 to 15% by weight, preferably 1 to 10% by weight.

20 [0026] The commercial synthetic sweetener products are generally small, i.e. less than 150 μm , in mean particle size, with particle not smaller than 150 μm accounting for at most 4% of the whole. Incorporation of such products markedly reduces the rate of disintegration of tablets. To improve the disintegration rate, the prior art employs a method which comprises incorporating a large amount of an excipient such as microcrystalline cellulose. However, incorporation of a large amount of such excipient according to said method results in an increase in tablet size, thereby making 25 the tablets difficult to take with ease. The present inventor found that when the particle size of a synthetic sweetener is increased or when a granulated mixture of a synthetic sweetener and light anhydrous silicic acid, hydrated silicon dioxide or the like is added, the rate of disintegration can be improved, namely prevented from retardation.

[0027] As a result, an invention was made of miniaturized tablets which can be easily taken as such and, when dropped into water in a glass, can rapidly self-disintegrate, enabling administration thereof in dispersion form.

30 [0028] When such a synthetic sweetener as saccharin, a salt thereof (e.g. saccharin calcium, saccharin sodium), cyclamic acid or a salt thereof (e.g. sodium cyclamate, calcium cyclamate, ammonium cyclamate) is used, said sweetener is required to be not less than 150 μm in mean particle size, preferably not less than 150 μm in particle size. In the case of a sweetener capable of producing a satisfactory bitter-masking effect in small amounts, for example aspartame, it is not always necessary that the mean particle size be not less than 150 μm , since the disintegrability of 35 tablets is little affected.

[0029] The synthetic sweetener may be incorporated either in the form of crystalline grains having a mean particle size of not less than 150 μm or in the form of a granulation product meeting the particle size requirement as obtained by wet granulation from the powder form small in mean particle size or by wet granulation or dry granulation from such powder together with a color additive and/or microcrystalline cellulose or a like excipient.

40 [0030] The granulation product containing light anhydrous silicic acid or hydrated silicon dioxide in addition to a synthetic sweetener can be produced by mixing the synthetic sweetener with 1 to 30% by weight, relative to the synthetic sweetener weight, of light anhydrous silicic acid or hydrated silicon dioxide and granulating the mixture in the conventional manner, if necessary using a binder and/or one or more other additives in common use. It was found that in the case of granulation products containing a synthetic sweetener together with light anhydrous silicic acid or hydrated 45 silicon dioxide, the particle size is not critical, with the result that the self-disintegrating properties are never adversely affected even when the mean particle size is below 150 μm . As regards other ingredients to be used in producing the tablets of this invention, the same ingredients or additives as used conventionally in the production of solid preparations may be mentioned. Thus, in addition to the above-mentioned synthetic sweetener or granulated synthetic sweetener, excipients such as microcrystalline cellulose, lactose, mannitol, starch, etc., flowability improvers such as light anhydrous silicic acid, hydrated silicon dioxide, etc., lubricants such as magnesium stearate, stearic acid, talc, etc., flavoring agents and other agents may be incorporated unless the self-disintegrating properties are adversely affected. When the β -lactam antibiotic has a large particle size, it may be ground prior to use. In this case, however, wet or dry granulation is required to improve the powder flowability in the step of compression.

50 [0031] In a preferred process for producing the tablets of the present invention, the above-specified disintegrator and binder, optionally together with other ingredients, are added to the β -lactam antibiotic, the mixture is granulated by a conventional method, the above-mentioned synthetic sweetener and/or granulated synthetic sweetener, optionally together with one or more other ingredients (e.g. flowability improver, lubricant, flavor), are then further added, and the resulting mixture is subjected to tabletting.

[0032] When, in the above production process, water is used for granulation in the granulation step, tablets with good self-disintegrating properties are generally obtained. In this connection, the inventor of this invention further found that when ethanol, isopropyl alcohol or a mixture of water and ethanol or isopropyl alcohol is used for granulation, tablets with good self-disintegrating properties and with very good dispersibility upon allowing dispersion in water can be obtained. The concentration of the aqueous solution of ethanol or isopropyl alcohol, which is suited for use, is 3 to 99% (volume/volume), preferably 10 to 60% (volume/volume).

INDUSTRIAL APPLICABILITY

[0033] The thus-obtained β -lactam antibiotic-containing tablets of this invention are small in size. For example, a tablet containing 400 mg potency (about 449 mg) of cefixime may weigh not more than 650 mg and a tablet containing 300 mg potency (about 307 mg) of cefdinir not more than 450 mg. They can be orally taken as such with ease. When they are to be taken by the aged, for instance, complaining of some difficulty in swallowing, in an aqueous dispersion form, the tablets can be rapidly disintegrated and dispersed in water.

[0034] Moreover, the use of ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol for granulation in the granulation step makes it possible to obtain tablets with still better dispersibility in water.

Test Example 1 (Disintegrator effect)

[0035] According to the formulation shown below in Table 1, cefixime bulk substance, microcrystalline cellulose, one of the disintegrators, light anhydrous silicic acid and magnesium stearate, taken in the respective specified proportions, were mixed up and the mixture was compressed on a single-punch tablet machine to give tablets having a diameter of 11 mm.

[0036] The tablets produced by the above method were evaluated for disintegration time in 1,000 ml of water ($20 \pm 1^\circ\text{C}$) using a Japanese Pharmacopeia disintegration tester, but without using any disk, with 30 cycles per minute of basket ascending and descending. The disintegration time data thus obtained are shown in Table 2.

Table 1

Cefixime bulk substance	448.9 (400 mg potency)
Microcrystalline cellulose	38.9
Disintegrator	38.9
Light anhydrous silicic acid	1.2
Magnesium stearate	5.9
Total	533.8 mg

Table 2

Disintegrator	Disintegration time (min.) n = 6
Carboxymethylcellulose calcium	1.2-1.3
Starch glycolic acid sodium	1.0-1.2
Crosslinked carboxymethylcellulose sodium	0.8-1.1
Low-substituted hydroxypropylcellulose	0.3-0.4
Crosslinked polyvinylpyrrolidone	0.3-0.4

[0037] As is evident from Table 2, those tablets which contain low-substituted hydroxypropylcellulose or crosslinked polyvinylpyrrolidone in accordance with the present invention disintegrate very rapidly.

Test Example 2 (Binder study)

[0038] According to the formulation shown below in Table 3, cefixime bulk substance micronized by a pin-type mill, microcrystalline cellulose and one of the binders, together with 50% (by volume) ethanol, were granulated in a high speed shear mixer, followed by drying under flowing air at 40°C for 17 hours and sizing through a 500- μm sieve. The granules sieved out were mixed with low-substituted hydroxypropylcellulose, light anhydrous silicic acid and magnesium stearate, in the respective specified proportions, followed by compression on a single-punch tablet machine, to

give tablets each having the specified weight and a diameter of 11 mm.

[0039] The tablets produced by the above method were evaluated for disintegration time under the same conditions as in Test Example 1. The disintegration time data thus obtained are shown in Table 4.

Table 3

Cefixime	448.9 (400 mg potency)
Microcrystalline cellulose	38.9
Binder	4.9 (14.6)
Low-substituted hydroxypropylcellulose	38.9
Light anhydrous silicic acid	1.2
Magnesium stearate	5.9
Total	538.7 mg (548.4 mg)

Table 4

Binder	% addition level (weight in mg)	Disintegration time (min.) n = 6
Polyvinylpyrrolidone	0.9 (4.9)	0.6-0.8
Polyvinylpyrrolidone	2.7 (14.6)	2.1-2.1
Hydroxypropylcellulose (L type)	0.9 (4.9)	1.4-2.0
Hydroxypropylmethylcellulose	0.9 (4.9)	1.0-1.5

[0040] As is evident from Table 4, the tablets produced by using polyvinylpyrrolidone, hydroxypropylcellulose (L type) or hydroxypropylmethylcellulose as the binder disintegrate rapidly.

Test Example 3 (Synthetic sweetener particle size study)

[0041] According to the formulation shown below in Table 5, cefixime bulk substance micronized by a pin-type mill, microcrystalline cellulose, low-substituted hydroxypropylcellulose and polyvinylpyrrolidone, together with 50% (by volume) ethanol, were granulated in a high speed shear mixer, followed by drying under flowing air at 40°C for 17 hours and sizing using a 500-µm sieve. The granules sieved out were mixed with light anhydrous silicic acid, magnesium stearate, strawberry powder flavor and commercial saccharin calcium, the large particle size saccharin calcium prepared in Example 1 to be mentioned later herein or the granulated mixture of saccharin calcium and light anhydrous silicic acid prepared in Example 2 to be mentioned later herein, in the respective specified proportions, followed by compressing on a single-punch tablet machine to give tablets each having the specified weight and a diameter of 11 mm.

[0042] The tablets produced by the above method were evaluated for disintegration time under the same conditions as in Test Example 1. The disintegration time data thus obtained are shown in Table 6.

Table 5

Cefixime	448.9 (400 mg potency)
Microcrystalline cellulose	38.9
Low-substituted hydroxypropylcellulose	38.9
Polyvinylpyrrolidone	4.9
Light anhydrous silicic acid	1.2
Magnesium stearate	5.9
Strawberry powder flavor	7.5
Saccharin calcium or granulated saccharin calcium	20.0
Total	566.2 mg

Table 6

Synthetic sweetener	Mean disintegration time (min.), n = 6
Saccharin calcium (mean particle size < 150 µm)	3.0
Saccharin calcium (particle size 150-840 µm)	0.6
Saccharin calcium-light anhydrous silicic acid mixture granulated (particle size 75-500 µm)	1.3

10 [0043] As is evident from Table 6, the tablets produced by using the saccharin calcium not less than 150 µm in particle size or the granulated mixture of saccharin calcium and light anhydrous silicic acid are positively shorter in disintegration time than the tablets produced by using the commercial saccharin calcium smaller than 150 µm in mean particle size.

15 Test Example 4 (Influence of the composition of the solution for granulation on the dispersibility of tablets)

20 [0044] A 2,200 ml portion of water or an aqueous solution of ethanol was used to granulate a mixture of 4,566 g of cefixime bulk substance micronized by a pin-type mill, 405 g of microcrystalline cellulose, 405 g of low-substituted hydroxypropylcellulose and 50.6 g of polyvinylpyrrolidone in a high speed shear mixer and, after drying under flowing air at 40°C for 17 hours, the granulation product was sized using a 500-µm sieve. The granules sieved out were mixed with 50.6 g of light anhydrous silicic acid, 101.2 g of magnesium stearate, 75.9 g of strawberry powder flavor and 202.6 g of saccharin calcium (particle size: 150-840 µm), followed by compressing on a rotary tablet machine to give oblong tablets each weighing 579 mg.

25 [0045] The tablets produced by the above method were evaluated, by the method mentioned below, for disintegration time as well as for dispersibility for use in dispersion form.

Disintegration time

30 [0046] The disintegration time evaluation was made in 1,000 ml of water (20 ± 1°C) using a Japanese Pharmacopeia disintegration tester, but without using any disk, with 30 cycles per minute of basket ascending and descending.

Dispersibility after standing of dispersions prepared

35 [0047] One tablet was dropped into 20 ml of water placed in a 50-ml beaker and the whole was allowed to stand for 5 minutes for self-disintegration. Then, the beaker was shaken gently for stirring and thereafter allowed to stand for 1 minute, followed by observation of the appearance.

Table 7

	Disintegration time (sec.)	Dispersibility after standing
Granulation using 50% ethanol	39	a
Granulation using 10% ethanol	84	a
Granulation using water	62	b
Flemoxin Solutab 500® (commercial product)	46	b

45 a : Wholly uniform in color, substantially without any precipitate.
b : A supernatant and a slight amount of a precipitate.

50 [0048] The tablets derived from the granules prepared using ethanol are still better in dispersibility after standing as compared with those derived from the granules prepared using water.

Test Example 5 (Disintegration test)

55 [0049] Test preparations A: Tablets produced in Example 1 to be mentioned later. B: Tablets produced in Example 7 to be mentioned later. C: Tablets produced in Example 8 to be mentioned later.

Test method

[0050] The disintegration time evaluation was performed in distilled water at $20 \pm 1^\circ\text{C}$ with 4 cycles per minute of basket ascending and descending, using an apparatus prescribed in the Japanese Pharmacopeia (12th edition) under Disintegration Test.

Test results

[0051]

- A: 1.13 minutes
 B: 1.30 minutes
 C: 1.02 minutes

[0052] The disintegration test results indicate that the test preparations A to C of this invention each shows good disintegrability.

EXAMPLE

Example 1

[0053] Water was added to saccharin calcium and the mixture was granulated by a conventional method, followed by drying, sieving and sizing to give saccharin calcium granules not less than 150 μm in particle size.

[0054] According to the formulation shown below, micronized cefixime bulk substance, microcrystalline cellulose, low-substituted hydroxypropylcellulose (L-HPC) and polyvinylpyrrolidone were weighed and mixed together, water was then added, and the mixture was granulated. The granulation product was dried under flowing air at 40°C for 17 hours and then sized using a 500- μm sieve. The granules sieved out were mixed with magnesium stearate, light anhydrous silicic acid, strawberry flavor and the above-mentioned granulated saccharin calcium according to the formulation shown below, followed by compressing on a single-punch tablet machine to give tablets each having the specified weight.

Table 8

Micronized cefixime bulk substance	448.9 mg (400 mg potency)
Microcrystalline cellulose (Avicel™ PH101; Asahi Chemical Industry)	38.9 mg
L-HPC (LH-21; Shin-Etsu Chemical)	38.9 mg
Polyvinylpyrrolidone (Kollidon™ 30; BASF)	4.9 mg
Light anhydrous silicic acid (Aerosil™; Tomita Seiyaku)	1.2 mg
Magnesium stearate	5.9 mg
Saccharin calcium (not less than 150 μm in particle size)	20.0 mg
Strawberry flavor	7.5 mg
Total	566.2 mg

Example 2

[0055] Saccharin calcium and light anhydrous silicic acid were mixed together in a ratio of 20:1 and then water was added. The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mixture of saccharin calcium and light anhydrous silicic acid (75-500 μm in particle size).

[0056] Then, tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8).

Example 3

[0057] Saccharin calcium and hydrated silicon dioxide were mixed together in a ratio of 20:1 and then water was added. The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mixture of saccharin calcium and hydrated silicon dioxide (75-500 μm in particle size).

[0058] Then, tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated

mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8).

Example 4

5 [0059] Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that L-HPC of Example 1 (Table 8) was replaced by the same amount of crosslinked polyvinylpyrrolidone (Kollidon™ CL; BASF).

Example 5

10 [0060] Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylcellulose (HPC-L; Nippon Soda).

15 **Example 6**

[0061] Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylmethylcellulose (TC-5R™; Shin-Etsu Chemical).

20 **Example 7**

25 [0062] According to the same formulation as that shown in Example 1 (Table 8), micronized cefixime bulk substance, microcrystalline cellulose, L-HPC and polyvinylpyrrolidone were weighed and mixed together, 50% aqueous ethanol was added, and the mixture was granulated. The granulation product was dried under flowing air at 40°C for 17 hours and then sized using a 500-µm sieve. The granules sieved out were mixed with magnesium stearate, light anhydrous silicic acid, strawberry flavor and the granulated saccharin calcium prepared in Example 1 (not less than 150 µm in particle size) and the resultant mixture was compressed on a single-punch tablet machine to give tablets having the same composition as that in Example 1 (Table 8).

30 **Example 8**

35 [0063] According to the formulation shown below, cefdinir-containing tablets were produced in the same manner as in Example 7.

Table 9

Micronized cefdinir bulk substance	306.8 mg (300 mg potency)
Microcrystalline cellulose (Avicel PH101®)	29.2 mg
L-HPC (LH-21)	29.2 mg
Polyvinylpyrrolidone (Kollidon 30®)	3.7 mg
Light anhydrous silicic acid (Aerosil®)	0.9 mg
Magnesium stearate	4.4 mg
Saccharin calcium (not less than 150 µm in particle size)	15.0 mg
Strawberry flavor	5.6 mg
Total	394.8 mg

Claims

- 50 1. A β-lactam antibiotic-containing tablet which comprises 60 to 85% by weight of a β-lactam antibiotic, 1 to 10% by weight of low-substituted hydroxypropylcellulose and/or crosslinked polyvinylpyrrolidone as a disintegrator and 0.5 to 2% by weight of a binder per tablet, said binder being polyvinylpyrrolidone, hydroxypropylcellulose or hydroxypropylmethylcellulose.
- 55 2. A tablet as claimed in Claim 1 which further comprises 0.5 to 15% by weight of a synthetic sweetener and/or a granulated synthetic sweetener.

3. A tablet as claimed in Claim 2, wherein the synthetic sweetener or the granulated synthetic sweetener has a mean particle size of not less than 150 µm.
4. A tablet as claimed in Claim 3, wherein the synthetic sweetener or the granulated synthetic sweetener is not less than 150 µm in particle size.
5. A tablet as claimed in any of Claims 2 to 4, wherein the granulated synthetic sweetener comprises a synthetic sweetener, and light anhydrous silicic acid and/or hydrated silicon dioxide.
10. A tablet as claimed in any of Claims 1 to 5, wherein the β-lactam antibiotic is cefixime or cefdinir.
7. A tablet as claimed in Claim 6, which contains 400 mg potency of cefixime, the tablet weight being not greater than 650 mg.
15. 8. A tablet as claimed in Claim 6, which contains 300 mg potency of cefdinir, the tablet weight being not greater than 450 mg.
9. A method of producing β-lactam antibiotic containing tablets according to any of claims 1 to 8 comprising the steps of granulating a mixture of a β-lactam antibiotic, a disintegrator, a binder and optionally excipients, 20 optionally mixing the granulated product with a synthetic sweetener and/or a granulated synthetic sweetener and further additives and compressing the mixture.
10. The method of claim 9, whereby the mixture is granulated using ethanol, isopropyl alcohol or a mixture of one of these with water.
25. 11. A method of preparing an aqueous dispersion containing a β-lactam antibiotic as the active ingredient by adding a tablet according to any of claims 1 to 8 to water.
30. 12. An aqueous dispersion containing a β-lactam antibiotic as the active ingredient prepared by the method of claim 11.

Patentansprüche

35. 1. Eine β-Lactam-Antibiotikum enthaltende Tablette, welche 60 bis 85 Gewichts-% eines β-Lactam-Antibiotikums, 1 bis 10 Gewichts-% niedrig substituierter Hydroxypropylcellulose und /oder vernetztes Polyvinylpyrrolidon als Desintegrator und 0,5 bis 2 Gewichts-% eines Bindemittels pro Tablette umfasst, wobei das Bindemittel Polyvinylpyrrolidon, Hydroxypropylcellulose oder Hydroxypropylmethylcellulose ist.
40. 2. Eine Tablette wie in Anspruch 1 beansprucht, welche weiter 0,5 bis 15 Gewichts-% eines synthetischen Süßungsmittels und/oder eines granulierten synthetischen Süßungsmittels umfasst.
3. Eine Tablette wie in Anspruch 2 beansprucht, worin das synthetische Süßungsmittel oder das granulierte synthetische Süßungsmittel eine mittlere Teilchengröße von nicht weniger als 150 µm hat.
45. 4. Eine Tablette wie in Anspruch 3 beansprucht, worin das synthetische Süßungsmittel oder das granulierte synthetische Süßungsmittel in der Teilchengröße nicht kleiner als 150 µm ist.
50. 5. Eine Tablette wie in einem der Ansprüche 2 bis 4 beansprucht, worin das granulierte synthetische Süßungsmittel ein synthetisches Süßungsmittel und leichte wasserfreie Kieselsäure und/oder hydratisiertes Siliciumdioxid umfasst.
6. Eine Tablette wie in einem der Ansprüche 1 bis 5 beansprucht, worin das β-Lactam-Antibiotikum Cefixime oder Cefdinir ist.
55. 7. Eine Tablette wie in Anspruch 6 beansprucht, welche 400 mg Wirkungsstärke von Cefixime enthält, wobei das Gewicht der Tablette nicht größer als 650 mg ist.

8. Eine Tablette wie in Anspruch 6 beansprucht, welche 300 mg Wirkungsstärke von Cefdinir enthält, wobei das Gewicht der Tablette nicht größer als 450 mg ist.
- 5 9. Ein Verfahren zur Herstellung β -Lactam-Antibiotikum enthaltender Tabletten gemäß einem der Ansprüche 1 bis 8, welches die Stufen umfasst Granulieren eines Gemisches eines β -Lactam-Antibiotikums, eines Desintegrators, eines Bindemittels und gegebenenfalls Hilfsstoffe, gegebenenfalls Vermischen des granulierten Produktes mit einem synthetischen Süßungsmittel und/oder einem granulierten synthetischen Süßungsmittel und weiteren Zusätzen und Verpressen des Gemisches.
- 10 10. Das Verfahren von Anspruch 9, wobei das Gemisch granuliert wird unter Verwendung von Ethanol, Isopropylalkohol oder eines Gemisches von diesen mit Wasser.
- 15 11. Ein Verfahren zur Herstellung einer wässrigen Dispersion, die ein β -lactam-Antibiotikum als Wirkstoff enthält, durch Zusatz einer Tablette gemäß einem der Ansprüche 1 bis 8 zu Wasser.
12. Eine wässrige Dispersion, die ein β -Lactam-Antibiotikum als Wirkstoff enthält, hergestellt mit dem Verfahren von Anspruch 11.

20 **Revendications**

1. Comprimé contenant un antibiotique à base de β lactam qui comprend de 60 à 85 % en poids d'un antibiotique à base de β lactam, de 1 à 10 % en poids d'hydroxypropylcellulose faiblement substituée et/ou de la polyvinylpyrrolidone réticulée en tant que désintegrateur et de 0,5 à 2 % en poids d'un liant par comprimé, ledit liant étant de la polyvinylpyrrolidone, de la hydroxypropylcellulose ou de la hydroxypropylméthylcellulose.
2. Comprimé selon la revendication 1 qui comprend en outre de 0,5 à 15 % en poids d'un adoucisseur synthétique et/ou d'un adoucisseur synthétique en granulés.
- 30 3. Comprimé selon la revendication 2, dans lequel l'adoucisseur synthétique ou l'adoucisseur synthétique en granulés a une taille moyenne de particule de pas moins de 150 μm .
4. Comprimé selon la revendication 3, dans lequel l'adoucisseur synthétique ou l'adoucisseur synthétique en granulés n'a pas une taille de particule inférieure à 150 μm .
- 35 5. Comprimé selon l'une quelconque des revendications 2 à 4, dans lequel l'adoucisseur synthétique en granulés comprend un adoucisseur synthétique, et un acide silicique anhydre et/ou un dioxyde de silicium hydraté.
6. Comprimé selon l'une quelconque des revendications 1 à 5, dans lequel l'antibiotique à base de β lactam est du céfixime ou du cefdinir.
- 40 7. Comprimé selon la revendication 6, lequel contient 400 mg potentiel de céfixime, le poids du comprimé n'étant pas supérieur à 650 mg.
8. Comprimé selon la revendication 6, lequel contient 300 mg potentiel de cefdinir, le poids du comprimé n'étant pas supérieur à 450 mg.
- 45 9. Procédé de production de comprimé contenant de l'antibiotique à base de β lactam selon l'une quelconque des revendications 1 à 8 comprenant les étapes de
granulation d'un mélange d'antibiotique à base de β lactam, d'un désintagrator, d'un liant et d'excipients optionnels,
de mélange optionnel du produit en granulés avec un adoucisseur synthétique et/ou un adoucisseur synthétique en granulés et d'autres additifs et de compression du mélange.
- 55 10. Procédé selon la revendication 9, grâce auquel le mélange est granulé en utilisant de l'éthanol, de l'alcool isopropyle ou bien un mélange de l'un de ceux-ci avec de l'eau.
11. Procédé de préparation d'une dispersion aqueuse contenant un antibiotique à base de β lactam en tant qu'ingrédient.

EP 0 890 359 B1

dient actif en ajoutant à de l'eau un comprimé selon l'une quelconque des revendications 1 à 8.

- 12.** Dispersion aqueuse contenant un antibiotique à base de β lactam en tant qu'ingrédient actif préparé au moyen du procédé de la revendication 11.

5

10

15

20

25

30

35

40

45

50

55